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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/644,221
Filing Date: August 19, 2003
Appellant(s): NAGAOKA, HITOSHI

Barbara E. Johnson
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 8/10/07 appealing from the Office action mailed 1/29/07.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

No amendment after final has been filed.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Pauwels, R., Antiviral Research, 71 (2006), pages 77-89

Amagase H. Treatment of hepatitis B patients with Lentinus edodes mycelia. In: New Trends in Peptic Ulcer and Chronic Hepatitis. Part II. Chronic Hepatitis. Princeton: Exerpta Medica 1987;316-2

Suzuki *et al.*, Biochemical and Biophysical Research Communications, Vol. 160, No. 1 (1989) pp. 367-37

**(9) Grounds of Rejection**

**WITHDRAWN REJECTIONS**

The following grounds of rejection are not presented for review on appeal because the examiner has withdrawn them.

The rejection under 35 U.S.C § 112, second paragraph regarding antecedent basis ONLY has been withdrawn.

The following ground(s) of rejection are applicable to the appealed claims:

**(a) The rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph, as failing to comply with the definiteness requirement.**

Claims 1 and 2 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague, indefinite and confusing in that the process requires that "at least one effective dose" of the extract "weakens HIV activity and inhibits HIV proliferation in said human". The recitation "at least one effective dose" is not clearly defined in the specification and there is no indication as to the amount that constitutes "at least one effective dose" to be administered. In addition, the specification indicates that the mycelium extract may be administered to the infected person without dilution or by "appropriately diluting". Yet no indication is found in the as-filed specification as to what amount of the extract, whether diluted or not, it to be administered or how. In addition, the amount of dilution is not set forth with any particularity.

**(b) The rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.**

Claims 1 and 2 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are broadly drawn to a method of treating a human infected with HIV by orally administering at least one effective dose, without amounts and concentrations. It is noted

that the at least one effective dose is never defined or identified in the instant written disclosure nor is the intended effect of the one or more doses clearly delineated. The length or frequency of treatment is not outlined with any particularity.

Moreover, applicant intends to treat a human infected with the human immunodeficiency virus. It is well recognized that HIV infections are notoriously difficult to treat. The effect of the administration of a *Lentinus edodes* extract is not predictable for this purpose. First, there is the issue of the exact preparation utilized. Not all *Lentinus edodes* extracts are identical, i.e., possess the same or substantially the same active ingredients, even if there is a minimum content of the unknown active ingredient(s), and they are prepared in the same or substantially the same method, and thus would not work identically. The method utilizes ranges of concentrations at least of water and degradative enzymes. The activities possessed by different fungal preparations would have different effects on different individuals, depending on their age, state of health, weight, sensitivity to allergens. Similarly, *Lentinus edodes* extracts would vary in their purity. In the instant case the size of the openings in the mesh do not appear to be indicated. In addition, Applicant does not disclose the *Lentinus edodes* strains necessary as the source of the extract.

Finally, applicants present as a single working embodiment the treatment of MT-4 cells infected with one particular strain of HIV. The data of Table 1, for example, show only inhibition of the HIV virus in MT-4 cells and not in living organisms. Thus, the in vitro "testing" done on the record fails to correlate with the treatment of a human as claimed with an "at least one effective dose".

Regarding the lack of necessary correlation between *in vitro* results and *in vivo* effects regarding the activity of an agent in the setting of HIV-infection see, e.g., Suzuki *et al.* (1989), page 372, paragraph 5. It is mentioned therein that issues such as bioavailability, metabolic features, and toxicities as well as other factors may negate the usefulness of a given agent. Specifically, the reference states:

> "It should be stressed, however, that the activity of an agent against HIV in vitro does not ensure that the agent will be clinically applicable in the setting of HIV-infection. Bioavailability, metabolic features, toxicities, and other factors may negate the usefulness of a given agent. LEM has been administered orally as a natural nutrient for over fifteen years in Japan and this history suggests that LEM might not bring about at least major side effects in human beings. However, it remains to be asked whether LEM can be absorbed orally to achieve the effective concentrations in plasma and whether LEM can exert its antiviral effect against HIV in the face of 100% plasma. Also we do not know how quickly LEM is degraded to lose its antiviral effect when introduced into the blood stream. Nevertheless, our findings

> described here and previous observations that EPS4 appears to have multiple biological activities including apparent immunopotentiating capability together with an activity against HIV in vitro warrant for further investigation."

Thus, the fact that *Lentinus edodes* has been administered orally as a natural nutrient for a long time in Japan, does not ensure that the extract as claimed will be effective in at least one dose to achieve effective concentrations in plasma, for example, by "administering at least one effective dose... to a human afflicted with a viral disease, wherein said viral disease is human immunodeficiency virus". Another issue to be considered is the degradation and loss of antiviral effects in the complex physiological environment of the human or animal body. Therefore, the results of the instant method of treating are unpredictable.

While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Applicant's attention is also directed to Pauwels (2006) which discusses the current state of the art with respect to the discovery of effective therapeutic agents and the challenges and difficulties of producing anti-HIV drugs that are effective, due to the complex nature of the virus, its variability and tendency towards becoming resistant to various treatments or drugs. See, e.g., pages 79 et seq.. At page 79 paragraph 2, it is stated in the context of some successful anti-HIV drugs which target areas such as the viral envelope, the HIV reverse transcriptase, the HIV protease mediate production of new enzymatic and structural HIV proteins that:

> "Despite these landmark achievements, a number of important therapeutic challenges remain. Some of them are directly related to the nature of HIV pathogenesis and others are reflecting short-comings of available therapies. HIV primarily infects $CD4^+$ T lymphocytes whereby continuous viral replication occurs throughout the course of the HIV disease (Coffin, 1996). Most CD4 cells turn over rapidly, but some belong to latent pools with long half-lives (Ho et al., 1995). Because of the viral reservoir function of long-lived target cell populations, antiviral agents are required to be administered over longer periods of time. The retroviral integration of the HIV genome into the host genome and the large and rapid HIV turnover combined with an error- prone replication process (mainly due to the RT step), explains the 'quasi-species' nature of HIV whereby the individual viral strains compete among themselves for survival and propagation (Fisher et al., 1988; Domingo et al., 2001). This capacity makes HIV well equipped to evolve viral variants that display various degrees of resistance to drug inhibition. A number of elements drive and influence this process of drug resistance development such as: (i) the extent of the viral dynamics and the level of ongoing HIV replication, (ii) the viral fitness, (iii) the presence, type, combination and frequency of viral variants that harbour one or more mutations that render the drug target less susceptible to drug inhibition, (iv) the type and use of drugs (e.g. mono-therapy, combination therapy) which exert a selection pressure and (v) the peak and through drug levels in the various tissues and compartments where the selection pressure occurs.

Thus, one of ordinary skill in the art would not have a reasonable expectation of success of treating a human infected with HIV by administering orally at least one effective dose of a purified, concentrated extract of *Lentinus edodes* of unknown composition, in the absence of a clear definition of what constitutes an "effective dose" and of an indication of how often and for how long such an oral dose is to be administered in order to achieve the stated purpose of weakening HIV activity and inhibit HIV proliferation in a human. There is nothing in this record to correlate the *in vitro* activity shown in the written disclosure for MT-4 cells with an administration protocol to achieve the claim designated effect in an *in vivo* setting in humans.

The scope of the claims is not commensurate with the teachings of enablement of the specification.

**(10) Response to Argument**

**(a) The rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph, as failing to comply with the definiteness requirement.**

Appellant's argue that the infusion as claim designated was already known as a healthy drink and the amount and route of administration for the composition of the present invention was already known and appreciated in the prior art. Appellants further argue that because the essence of the present invention is not in the preparation and general administration of the *Lentinus edodes* infusion, but, rather, the new and unexpected identification of the medical indications, notably, anti-HIV, the administration of the *Lentinus edodes* infusion has an indication-specific medicinal effect even when given according to prior art dosages and routes of administration.

However, Appellant fails to appreciate the claims as written specifically require administration of "at least an effective dose" for the particular purpose of treating a patient infected with HIV, and achieve the stated purpose of weakening HIV activity and inhibiting HIV proliferation in a human. Appellant has not proffered prior art disclosing or discussing the administration of particular infusions or protocols for this purpose. Thus, there is no clear definition of the record of what constitutes "at least one effective dose" in the context of the claimed invention.

Appellant further alleges that those skilled in the art of *Lentinus edodes* infusions would know what constitutes an effective dose, because the method of preparation is clearly disclosed. Moreover, appellant alleges that the composition is administered in "beverage amounts". Appellant states that this involves "a few to several ounces" per administration. Yet the specification does not appear to direct one of ordinary skill in the art to dispense beverage amounts beyond mentioning in the Summary of the Invention discussing the prior art:

> "In these publications, however, there is neither description nor suggestion on that the obtained healthful drinks are effective as inhibitors against Hepatitis B virus or HIV activity."[0009].

There is no guidance in the as-filed specification as to how one of ordinary skill in the art is to determine the amount to be used in each individual human to be treated with the "infusion" therapy or how often the composition is to be administered to achieve the required effect. Appellant does not indicate the basis for "a few to several ounces" as alleged. Moreover, the specification does not appear to address this issue. It must be remembered that the claims are not drawn to a beverage infusion to be consumed by a healthy individual or a person suffering from some unidentified malaise or ailment. The claims are drawn specifically to a **method of treating HIV**, a disease that is universally recognized to be difficult to treat and which is generally deadly. The claims as written require the specific effect of "weakening of HIV activity and inhibition if HIV proliferation in a human" without precise and specific guidelines as to how the treatment is to be administered. The issue is not what constitutes oral administration as addressed by appellants, but rather the issue is whether one of ordinary skill in the art can readily determine what constitutes an "at least one effective dose" in the instant context specifically and particularly to treat HIV in the manner claimed and the protocol to follow in the context of "at least" one unidentified effective dose, i.e., frequency of administration and length of treatment.

That the claims are interpreted in light of the specification is recognized. However, there is no guidance in the specification to aid in this regard. There is no clear nexus between "an effective dose" and "beverage amounts" as argued. And even if there were a correlation, the written disclosure of this application fails to address the issues of the precise preparation to be provided and the actual amounts thereof required to be administered as well as the precise administration protocol required to achieve the results claimed of weakening of HIV activity and

inhibition if HIV proliferation in a human. There is no indication as to whether the alleged and undefined "beverage amounts", for example, are to be administered on a daily basis, on an hourly basis, or on a weekly basis, for example. Similarly there is no indication as to whether the regime is to be repeated for a week, a month, a year, or for the lifetime of the individual, for example.

Therefore, considering the seriousness of the viral infection involved and considering the required effect of weakening of HIV activity and inhibition if HIV proliferation in a human, it is deemed that the claims fail to meet the definiteness requirement.

While the Sawadaishi declaration indicates that the oral dose of 2 g daily was administered in the treatment of Hepatitis B, a virus unrelated to HIV, the length of treatment is not revealed and there is no clear nexus between the results in the declaration pertaining to 2 g daily of an extract powder and the claim designated recitation of "at least one effective dose" to be administered orally to weaken HIV activity and inhibit HIV proliferation in a human infected with HIV. See also the discussion *infra.*

Declarations directed to the administration of a composition for the treatment of an unrelated virus in a different patient fail to obviate the rejection.

Therefore, it is submitted that the claims fail to meet the definiteness requirement.

**(10) Response to Argument**

**(b) The rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.**

Appellant's argues that the infusion as claim designated was already known as a healthy drink and the amount and route of administration for the composition of the present invention was already known and appreciated in the prior art. Appellants further argue that because the essence of the present invention is not in the preparation and general administration of the *Lentinus edodes* infusion, but, rather, the new and unexpected identification of the medical indications, notably, anti-HIV, the administration of the *Lentinus edodes* infusion has an indication-specific medicinal effect even when given according to prior art dosages and routes of administration. Appellant concludes that the effective dose can be equated with "healthy drink" dose or a beverage amount dose.

Yet the specification does not appear to direct one of ordinary skill in the art to dispense beverage amounts beyond mentioning in the Summary of the Invention discussing the prior art:

> "In these publications, however, there is neither description nor suggestion on that the obtained healthful drinks are effective as inhibitors against Hepatitis B virus or HIV activity."[0009].

There is no guidance in the as-filed specification as to how one of ordinary skill in the art is to determine the amount to be used in each individual human to be treated with the "infusion" therapy or how often the composition is to be administered to achieve the required effect.

In response, it is noted that the present invention specifically requires that "at least an effective dose" succeed in treating a patient infected with HIV to weaken HIV activity and inhibit HIV proliferation in the human patient. Appellant has not proffered prior art disclosing or discussing the administration of particular infusions or protocols for this purpose. Appellant has not indicated with any precision what constitutes "a typical effective dose in herbal pharmaceutical practice" or provided experimental data to substantiate these contentions. Also there is no indication on this record as to the administration protocol of "at least one effective dose" to a human patient infected with the human immunodeficiency virus wherein weakening HIV activity and inhibiting HIV proliferation may be ascertained.

Appellant alleges that those skilled in the art of *Lentinus edodes* infusions would know what constitutes an effective dose, because the method of preparation is clearly disclosed. Moreover, appellant alleges that the composition is administered in "beverage amounts". Appellant states that this involves "a few to several ounces" per administration, without an indication in the as filed written disclosure as to how a determination, in fact, is to be made by one of ordinary skill in the art as to the amount to be used for each individual human to be treated with this therapy or how often the composition is to be administered to achieve the required effect. Appellant does not indicate the basis for "a few to several ounces" as alleged. Moreover, the specification does not appear to address this issue. It must be remembered that the claims are not drawn to a method of administering a beverage infusion to a healthy individual or to a person suffering from some unidentified malaise or ailment. The claims are drawn specifically to a **method of treating HIV**, a disease that is universally recognized to be difficult

to treat and for which the specific results of weakening of HIV activity and inhibition if HIV proliferation in a human are required as claim designated.

The issue is not what constitutes oral administration as addressed by appellants, but rather the issue is whether or not it would require undue experimentation for one of ordinary skill in the art to determine what constitutes "at least one effective dose" in the instant context specifically and particularly to treat HIV in the manner claimed. The issue of the treatment of HIV cannot readily and dismissively equated with any treatment in herbal medicine.

Applicant's statements regarding the interchangeability of all *Lentinus edodes* strains for the purpose of this invention are noted. However, there is no evidence provided for the unsubstantiated allegations that the unidentified strain used is exemplary of all *Lentinus edodes* strains.

In addition, the results of the Sawadaishi declaration pertaining to treatment of hepatitis B are cited in an attempt to extrapolate to a weakening of HIV activity and inhibition of HIV proliferation in a human when the extract is administered orally in at least one effective dose.

However, in that declaration fifty-eight patients having acute or chronic hepatitis B (HBV) were given 2 g daily of an *Lentinus edodes* mycelium extract powder in the form of a drink. The length of the treatment is not revealed, i.e., whether it was performed for two days, 15 days, 30 days, several months or several years. In addition, it cannot be determined whether or not the powder administered is the same the extract as claimed designated, since the extract in claims 1 and 2 is not dried and is not in powder form.

It is noted that the mechanisms of action of HIV and HBV are different. HIV and HBV are different types of viruses, HIV is a retrovirus, i.e., an RNA virus (a virus composed not of DNA but of RNA). Retroviruses have the enzyme reverse transcriptase to transcribe RNA (their RNA) into DNA. The retroviral DNA can then integrate into the chromosomal DNA of the host cell to be expressed there with an RNA. After initial contact and attachment of HIV to a cell of the immune system (e.g. lymphocytes, monocytes), there is a cascade of intracellular events. The endproduct of these events is the production of massive numbers of new viral particles, death of the infected cells, and ultimate devastation of the immune system. In contrast, the hepatitis B virus belongs to a family of DNA viruses called Hepadnaviridae. These viruses primarily infect liver cells.

virus belongs to a family of DNA viruses called Hepadnaviridae. These viruses primarily infect liver cells.

The results of the declaration indicate that the treatment was effective and the patient's response to treatment was evaluated by measuring serum levels of GOT and GPT enzymes as well as serum levels of hepatitis B "e" (Hbe) antigens and antibodies (a known marker for hepatitis B virus infection). The relevance of these results to the method as claimed is unclear, since no correlation is proffered to equate or correlate the touted method of treating HBV with the present treatment of a human infected with HIV wherein the immune system has been ravaged due to HIV.

There is nothing in the record or declarations presented to proffer sufficient and specific guidance to one of ordinary skill in the art regarding the protocol required for the treatment of a human infected with the human immunodeficiency virus (HIV) with a preparation comprising a *Lentinus edodes* extract, the contents of which are not defined with any precision and wherein no active ingredients are identified or standardized. The pharmaceutical composition is characterized only by its method of preparation and its effectiveness *in vitro* with MT-4 cells. The mode of administration is oral, but the dosage to be administered is not defined or identified and is merely indicated as "at least one effective dose". No protocol is identified for oral administration of the extract to treat a human infected with the human immunodeficiency virus (HIV) such that the extract weakens HIV activity and inhibits HIV proliferation *in vivo* in a human infected with HIV. A protocol of administration to MT-4 cannot be extrapolated to humans and applicants have failed to provide appropriate guidance in the as-filed written disclosure about the concentration of "beverage" to be administered as well as for the frequency and length of treatment encompassed by "at least one dose".

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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